United States
Environmental Protection Agency

Office of Research and Development
US Environmental Protection Agency
Multi-Year Plan (FY 2003-2008) For

Safe Food

April 15, 2003

Not Yet Externally Peer Reviewed

The Office of Research and Development's (ORD) multi-year plans (MYPs) present ORD's proposed research (assuming constant funding) in a variety of areas over the next 5-8 years. The MYPs serve three principal purposes: to describe where our research programs are going, to present the significant outputs of the research, and to communicate our research plans within ORD and with others. Multi-year planning permits ORD to consider the strategic directions of the Agency and how research can evolve to best contribute to the Agency's mission of protecting human health and the environment.

MYPs are considered to be "living documents." ORD intends to update the MYPs on a regular basis to reflect the current state of the science, resource availability, and Agency priorities. ORD will update or modify future performance information contained within this planning document as needed. These documents will also be submitted for external peer review.

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MULTI-YEAR PLAN
April 15, 2003
Safe Food Multi-Year Plan
U. S. Environmental Protection Agency
Office of Research and Development
Washington, D.C. 20460

Executive Summary

This Safe Food Multi-Year Plan (MYP) describes the Office of Research and Development's (ORD) problem driven research program that addresses the Office of Prevention, Pesticides and Toxic Substances (OPPTS), Office of Pesticide Program's (OPP) highest priority pesticide research needs in support of the Food Quality Protection Act (FQPA). To be responsive, ORD will provide timely pesticides research results relevant to the tolerance reassessments immediately as these results become available, with all this research culminating to meet OPP's Congressional mandate to reassess pesticide tolerances for current use (August 1996) pesticides by August 2006. ORD will consult with OPP on a regular basis to identify the specific pesticides and associated research topics of highest priority for the future research program. ORD will initially investigate these problems using four broad research themes to meet the requirements of the Food Quality Protection Act. They will focus on ways to help OPP decide how best to a) evaluate aggregate risks; b) evaluate cumulative risks, c) apply 10X safety factors to protect children and other sensitive populations and d) to use physiologically-based pharmacokinetic (PBPK) data and models to refine their risk assessments and decisions regarding pesticide safety. As these issues are addressed and the results are provided to OPP, ORD's research program will shift emphasis to identifying the underlying default assumptions used in these methods and models. These initial models will be refined using selected pesticides with known modes-of-action.

This MYP provides the current direction for achieving the single Long-Term Goal (LTG) defined by ORD for its Safe Food research program which is **"By 2008, provide scientific tools to OPP/OPPTS that can be used to characterize, assess, and manage risks across the exposure-to-dose-to-effects continuum in implementing the FQPA requirements"**. ORD has identified nine critical lines of work (Annual Performance Goals (APG)) that must be completed by FY 2008 to meet the LTG. Progress towards meeting these goals will be measured by Annual Performance Measures (APMs) as defined later in this document. The APGs are:

- Deliver state-of-the-science tools (methods, models, approaches) and quality exposure data for characterizing aggregate risks from exposure to pesticides to OPP in order to reduce uncertainty in risk assessments under FQPA
- Analysis of needs and research strategy for developing tools and data to characterize cumulative exposures/risks for pesticides

- Develop framework and analysis of research needs for using PBPK data and models in

risk assessment
- Provide sound science that supports the August 2006 reassessment of pesticide tolerances
- Dose response research that addresses cumulative exposures/risks and the hypothesis of dose additivity for pesticide mixtures
- Provide risk assessors and managers with approaches for using PBPK data and models in risk assessment
- Evaluate 10X safety factors for new pesticides for aggregate exposure/risk
- Develop tools and data to characterize cumulative exposures/risks for current use and emerging pesticides, including lifestage and temporal variability
- Develop guidance for using PBPK data and models to support risk assessments

Introduction

The Office of Research and Development (ORD) initiated a multi-year planning process in Fiscal Year 2001 (FY 01) to plan the direction of its research in selected topics over the next five to ten years. Multi-Year Plans (MYPs) are being developed, revised, and implemented on a yearly basis to help ORD focus its current and future research on the highest priority issues and promote an integrated approach to achieving the Agency's long-term research goals.

The MYPs provide a framework that integrates research across ORD's laboratories and centers in support of the Agency's mission to protect human health and to safeguard the natural environment. There are sixteen ORD MYPs aligned with the Environmental Protection Agency's (EPA) Government Performance and Results Act (GPRA) goals. Each MYP is composed of: a narrative description of the plan and how the research is being developed to achieve one or more Long-Term Goals (LTG); flow diagrams outlining the sequence and relationships of the Annual Performance Goals (APG) aligned under each LTG; and tables describing the Annual Performance Measures (APM) and milestones that comprise each APG.

The Safe Food MYP sets forth ORD's strategy for planning and conducting research in support of ORD's Safe Food: Food Quality Protection Act (FQPA) research program, and arrays ORD's research plans for the period FY 03-08. It provides a focused, problem driven research framework and direction, reflective of available ORD scientific capabilities and capacity. Most importantly, it is responsive to the highest priority research and programmatic needs identified by EPA's Office of Pesticides Programs (OPP) of the Office of Prevention, Pesticides, and Toxic Substances (OPPTS) in implementing the requirements outlined in the FQPA (1996). The Safe Food research outlined in this MYP is designed with sufficient flexibility to address OPP/OPPTS's current and emerging high priority scientific issues and questions.

The Safe Food MYP supports all five goals of ORD's Strategic Plan: 1) support the Agency's Mission; 2) be a high-performing organization; 3) be a leader in the environmental research community; 4) integrate environmental science and technology to solve environmental problems; and 5) anticipate future environmental issues. This MYP promotes integration and

collaboration of the technical skills, expertise, capabilities, and resources contained within the

ORD laboratories and centers.

While there isn't a specific Safe Food research strategy, three ORD research strategies address relevant research: the external review draft *Human Health Research Strategy* prepared for ORD's Science Advisory Board review (USEPA 2002a) (www.epa.gov/nheerl/hhrs/); the *Strategy for Research on Environmental Risks to Children* (www.epa.gov/ORD/WebPubs/final) (USEPA, 2000); and the *Research Plan for Endocrine Disruptors* (www.epa.gov/ORD/WebPubs/final/revendocrine.pdf) (USEPA, 1998). For planning purposes, the Safe Food budget is assumed to be constant through FY 08 at approximately $9 million per year.

This document provides an overview of ORD's research program in support of Safe Food. Specific task level details associated with the individual research activities outlined in this MYP are available through the corresponding ORD laboratory and center implementation plans.

This MYP begins with this introduction and a brief background section. These lead-in sections are followed by sections on: the Safe Food science issues; OPP/OPPTS research needs for implementing FQPA; the approach employed for selecting and prioritizing future ORD research activities in support of OPPTS highest priority FQPA research needs; the Safe Food LTG, APGs, and APMs; research accomplishments during FY 00-02; research being planned and conducted within Safe Food; and research being conducted by other EPA and Federal Agency programs, including linkages of the Safe Food with these other research programs.

Background

On August 3, 1996, the Food Quality Protection Act (FQPA) was signed into law, amending the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to require tolerance reassessment during re-registration. The law also states that by August 2, 2006, EPA must review all pesticide tolerances and exemptions for pesticide chemical residues that were in effect prior to FQPA enactment, and ensure that they are protective of children. FQPA also amends the Federal Food, Drug and Cosmetic Act (FFDCA) to require a safety finding in the tolerance reassessment, based on factors including an assessment of cumulative effects of chemicals that share a common mechanism of toxicity, an assessment of aggregate dietary and all other non-occupational sources of exposure, and an assessment of toxicity to infants and children. Additionally, FQPA requires EPA to periodically review pesticide registrations, with a goal of establishing a 15-year cycle, to ensure that all pesticides meet updated safety standards.

The implementation of FQPA required the Agency to revisit some of its existing policies relating to the determination and regulation of dietary risk, and also raised a number of new issues for which policies needed to be created. OPP/OPPTS developed and refined these policies in collaboration with other Agency offices and programs and with outside parties composed of representatives from industry, environmental groups, and other interested entities. The following

science policy issues were identified as key to the implementation of FQPA and the pesticides tolerance reassessment:

- Application of the FQPA 10-Fold Safety Factor
- Whether and How to Use "Monte Carlo" Analyses in Dietary Exposure Assessments
- How to Interpret "No Detectable Residues" in Dietary Exposure Assessments
- Refining Dietary (Food) Exposure Estimates
- Refining Dietary (Drinking Water) Exposure Estimates
- Assessing Residential Exposure
- Aggregating Exposure from all Non-Occupational Sources
- How to Conduct a Cumulative Risk Assessment for Organophosphate or Other Pesticides with a Common Mechanism of Toxicity
- Selection of Appropriate Toxicity Endpoints for Risk Assessments of Organophosphates
- Whether and How to Use Data Derived from Human Studies

One of the most important policies relates to the application of the FQPA 10-fold Safety Factor (US EPA 1999a,b), commonly referred to as the children's 10X Safety Factor. FQPA provides that in making a finding of reasonable certainty of no harm for threshold effects, "an additional 10-fold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of data with respect to the exposure and toxicity of infants and children." The Administrator may use a different margin of safety "only if, on the basis of reliable data, such margin will be safe for infants and children."

EPA's policy document (USEPA 2002b) and reports developed by the Agency 10X Task Force (USEPA 1999a,b) discuss areas of uncertainty and recommendations for improving the toxicity and exposure databases which support decisions on when to apply the 10X Safety Factor. USEPA (1999a,b) also discuss the need for new toxicity tests to provide more comprehensive coverage of life stages, a more systematic evaluation of structural and functional toxicity in the young, and a more complete exposure database. Over the past three years, ORD has been implementing the recommendations of the 10X Task Force. They have been considered in developing this Safe Food MYP.

Research being planned and conducted under the Safe Food MYP builds on ORD's former Pesticides and Children Research Program. The research program being implemented prior to the establishment of the MYP planning process was designed to address critical issues associated with pesticide exposures to infants and children. This new MYP-driven research program is intended to reduce the uncertainties in future risk assessments conducted under the FQPA. It takes into consideration the science policy issues identified as a result of the FQPA (e.g., susceptibilities of children, and aggregate/cumulative exposures and risks), as well as recommendations arising from various reports on pesticides, risk assessment, and risk management (the 1993 National Research Council (NRC) report *Pesticides in the Diets of Infants and Children*, the1994 NRC report *Science and Judgment in Risk Assessment*, and the 1996 draft report by the President's Commission on Risk Assessment & Risk Management *Risk*

Assessment and Risk Management in Regulatory Decision-Making). These reports have suggested that EPA's current approaches to risk assessment do not adequately account for cumulative risks arising from complex exposure patterns and human variability due to age, sex, pre-existing disease, health status, nutritional status, and genetic predisposition. In addition, EPA's Science Advisory Board has identified some of the scientific limitations facing the Agency. Exposure assessments are limited "...by technical limitations in the currently available exposure measurement techniques, by severe limitations of the currently available databases containing exposure and exposure-relevant data, by reliance on numerous assumptions which have been proven incorrect or are not supported by common experience and/or direct observations, and by the current fragmentation and lack of coherence of available models for different media, pathways, chemicals, etc..."

As described in the draft *Human Health Research Strategy (HHRS)*, ORD is developing an integrated multidisciplinary research program that addresses high priority science questions and uncertainties that lie along a continuum from source through exposure and dose to adverse outcomes or disease (Figure 1). ORD recognizes that questions related to assessing aggregate and cumulative risk and evaluating risks to children are complex and will require an integrated approach to understand the linkages along the continuum. For example, a way to reduce uncertainties associated with the risk assessments for children exposed to pesticides is to understand: which pesticides children are exposed to; the frequency, duration, and magnitude of these exposures; and the key pharmacokinetic (PK) and pharmacodynamic (PD) factors that make children different from adults in their health responses to pesticide exposure. In addition, an integrated ORD research program will be crucial for developing methods to estimate risks using biomonitoring data reported from large-scale exposure and epidemiological studies currently being planned and conducted by ORD's National Exposure Research Laboratory (NERL) and National Health and Environmental Effects Research Laboratory (NHEERL), the National Centers for Children's Environmental Health and Disease Prevention (collaborative research programs jointly sponsored by EPA and the National Institute for Environmental Health and Safety (NIEHS)), and the Centers for Disease Control and Prevention (CDC). The research being planned within this MYP and other ORD MYPs supporting the HHRS is critical for the design and effective implementation of the proposed National Children's Study, an Interagency Study being developed under the joint leadership of the National Institute of Child Health and Human Development (NICHD), CDC, and EPA.

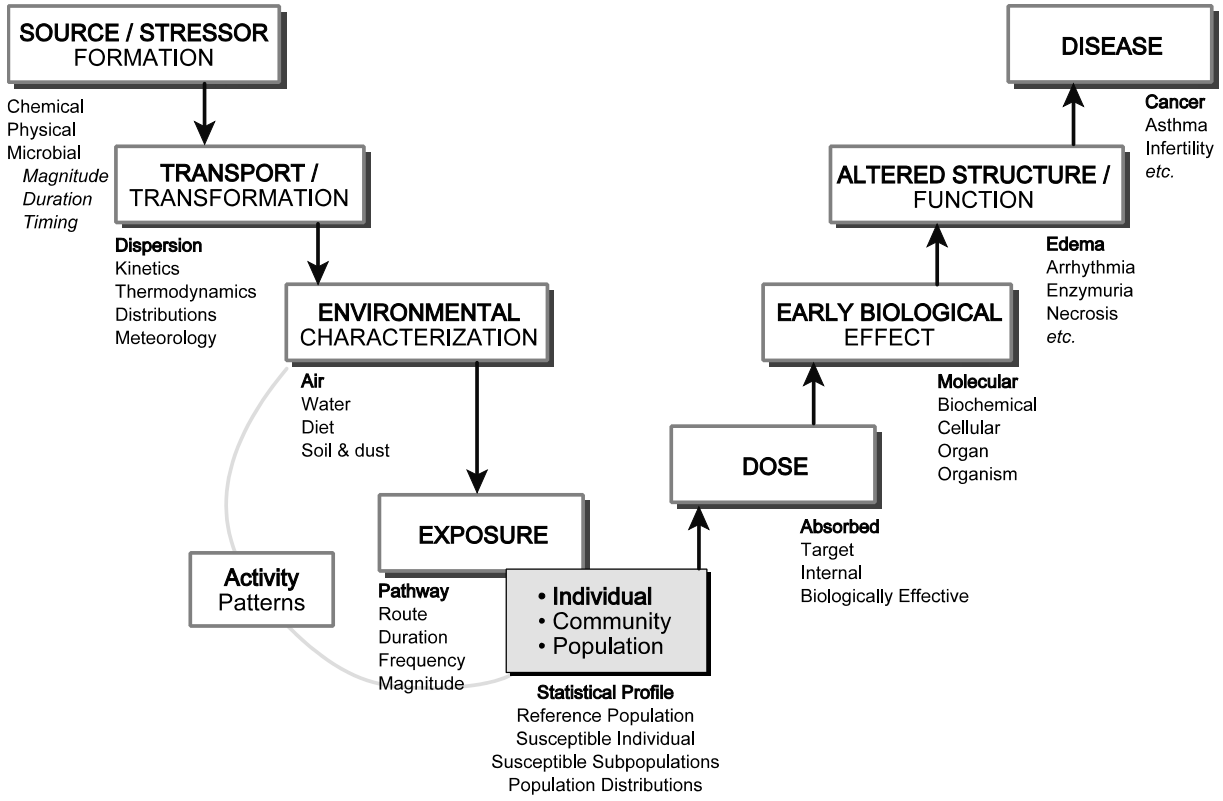
Science Issues

Research needs related to the FQPA fall into two broad categories: 1) risks to children from exposure to pesticides, and 2) cumulative risks from exposure via multiple pathways to pesticides with common modes of action. Research is needed to improve the databases for assessing key factors influencing children's exposure and the corresponding toxicity of pesticides for infants and children. This reinforces the need to conduct research on children's exposures

and risks as highlighted in the 1993 NRC report, as children appear to be differentially sensitive

to some chemical exposures.

Figure 1. Scientific Elements of Human Health Risk Assessment



Windows of vulnerability exist during development, particularly during early gestation, but also throughout pregnancy, infancy, childhood, and adolescence, when toxicants may permanently alter the function of a system. Children may be more vulnerable than adults because of differences in absorption, metabolism, distribution storage, and excretion, with these often resulting in higher biologically effective doses to target tissues. Children can be more highly exposed than adults because of proportionately higher food intake and breathing rates, different diets, and activities (e.g., playing on floors) that result in greater contact with environmental contaminants. Health threats to children are often difficult to recognize and assess because of our limited understanding of when and why children's exposures and responses are different from those of adults. Detailed research needs related to the susceptibility of children are described in ORD's *Strategy for Research on Environmental Risks to Children* (USEPA, 2000a).

Improved tools (methods, data, models, risk assessment guidance, and toxicity testing methods and protocols) are needed for assessing aggregate and cumulative risks across the exposure-to-dose-to-effects continuum that result from children's multimedia, multipathway exposures to pesticides with like mechanisms of action, as defined under FQPA. For purposes of this MYP, aggregate risks are defined as risks experienced by an individual exposed to a single pesticide via all relevant routes, pathways and sources. Cumulative risks are defined as risks experienced by an individual exposed to multiple pesticides having a common mode of action accumulated over time, over all routes, pathways, and sources. Research is needed to understand the magnitude and extent of exposures of pesticides used on food, along with non-occupational pesticide exposures in and around residential environments and other indoor/outdoor environments. Special emphasis should be placed on characterizing exposures and the corresponding critical factors influencing these exposures in those environments where young children spend the majority of their time. Better methods of estimating internal doses in target tissues through the use of pharmacokinetic approaches are needed to perform aggregate and cumulative assessments and to take into account age-related differences in physiology and metabolism. Research is also needed to understand the co-occurrence of exposure to pesticides and other chemicals with like mechanisms of action, the interactions between chemicals (especially pesticides) that result in increased or decreased toxic response, and the methods by which cumulative risk to chemicals (especially pesticides) with like mechanisms of action may be assessed.

FQPA Research Needs

Senior ORD, OPPTS, and OPP science managers and scientists met for their second annual research planning workshop on October 9, 2002, to discuss OPP/OPPTS' problem-driven research needs for FQPA implementation. During this meeting, OPP/OPPTS reviewed and updated their time lines (Table 1) for reviewing pesticides tolerance levels. While the initial focus remains on the FQPA 2006 requirement to conduct pesticide tolerance reassessments, OPP/OPPTS, recognizing that this is not a one-time process, outlined tentative out-year target dates for reviewing other pesticide tolerance levels.

Appendix 1 summarizes OPP/OPPTS' research needs as reconfirmed in the October 9 meeting. This research agenda outlined in this appendix, which remains virtually unchanged from FY 02, serves as the springboard for ORD's current Safe Food FQPA research program. OPP/OPPTS attempted to separate their research needs into two categories, those addressing children's risk and those addressing aggregate and cumulative risk. There is considerable overlap in the fundamental science that addresses both of these FQPA implementation areas. For planning purposes, ORD first merged both sets of needs into cross-cutting research topics (**OPP/OPPTS PROGRAMMATIC NEEDS**), subsequently categorized these by major research topic ***(bold italics)***, and finally listed each by ORD research activity (bullet statements) within each research topic.

Table 1. OPP/OPPTS Time Lines	
WHAT	**WHEN**
pyrethroids	by early 2004
methyl-carbamates	by early 2004
[a] Reassessment of current use pesticide tolerance levels	August 3, 2006
conazoles	2006-2010
endocrine disrupting pesticides	2006-2010
triazines	2010

[a] OPP anticipates that these reassessments may continue after the August 3, 2006 timetable.

At the October 9, 2002 meeting, there was a discussion regarding how to best align the Safe Food MYP research with OPP's FQPA time lines and mandates. OPP noted that all the areas were important and expressed the need for both short-term and long-term research and for periodic regulatory technical support. The completion of the current use pesticide tolerance reassessments in 2006 will not end OPP's risk assessment activities, and the need for additional ORD research in this area will continue. To be responsive to OPP's needs, ORD will provide pesticides research results relevant to the tolerance reassessments immediately as these results become available, with all of ORD's research through FY 05 culminating to achieve the 2005 Annual Performance Goal (APG 42: Provide sound science that supports the 2006 reassessment of pesticide tolerances). ORD will continue to consult with OPP on a regular basis to identify the pesticides of highest priority for the future research program. ORD already follows this approach as evidenced by shifts in research emphasis from organophosphate pesticides to carbamates and pyrethroids. ORD will also begin or continue studying conazoles, triazines, and endocrine disrupting pesticides, all the pesticides that OPP will assess in the period 2006-2010. OPP recognizes the need for selected research activities to continue on some well-studied pesticide classes where their initial time lines have already ended such as the organophosphates. OPP supports this additional research that will develop the methods, data, and models to fill critical data gaps and ultimately be used to provide tools that will be applicable to a wider range of pesticide classes.

In 2002, the Agency sought to strengthen the scientific basis of its decisions by having ORD become more fully involved in decisions that involve science issues. EPA named the ORD Assistant Administrator as the Agency Science Advisor and designated ORD as a core EPA Office with responsibilities for concurrence on the scientific aspects of regulatory decisions similar to the Office of General Counsel's role in concurring in the legal aspects. ORD was also given more of a role in non-regulatory decisions. This resulted in an increased level of ORD technical support for the Program Offices through participation on work groups, review of

documents, consultation, and short-term research. These requests depend on the day-to-day needs of the Program Offices and cannot be predicted in the MYP.

FY 2000 - FY 2002 Research Accomplishments

Over the period FY 00 - 02, the ORD Safe Food research program provided OPP/OPPTS with a variety of improved tools for assessing children's aggregate risks to pesticides. Through a variety of APMs and other less formal products, ORD transferred to OPP new and improved skills, techniques, and knowledge that will ultimately support OPPTS's meeting the FQPA mandates and ORD's accomplishment of the overarching LTG. In FY 00, OPP was provided a set of methodologies for evaluating risks posed by food-use products. A first generation multimedia, multipathway exposure model for infants and young children was provided and used to initially identify critical pathways and factors influencing children's exposures to pesticides. Initial research was completed characterizing children's dietary exposures that may result with routine processing and handling of food products. And an improved modeling module for NERL's Dietary Exposure Potential Model was developed that allows risk assessors to estimate dietary exposures and relate these to potential sources.

Through eight FY 01 APMs, ORD provided OPP with high quality exposure and effects data, innovative risk assessment methods and models, and data for the development of future control technologies needed to comply with the FQPA. High quality children's exposure and exposure factor data from NERL's NHEXAS and Children's Total Exposure to Pesticides and Other Persistent Pollutants (CTEPP) field studies were provided to OPP, filling critical data gaps and reducing the risk assessors' reliance on default assumptions. The data were also submitted to NCEA for inclusion in the Exposure Factor's Handbook. Based on lessons learned through previous studies, new and improved field and analytical methods as well as a comprehensive exposure field measurement protocol were developed to generate critical data for future risk assessments. An in-vitro screening tool that rapidly identifies toxic pesticides for the young was developed. Effects study results categorizing age-dependent differences in response to one or more pesticides following repeated chlorpyrifos exposures was provided to OPP to help address critical developmental issues for understanding and managing children's risks to pesticides. The Stochastic Human Estimating Dose Simulation (SHEDS) model was upgraded to account for both variability and uncertainty in estimating children's aggregate pesticide exposures. This model has since been used by OPP to assess children's risks to chlorpyrifos and chromated copper arsenic (CCA) treated wood.

In FY 02, ORD continued to provide OPP with high quality exposure and effects data and tools in support of the August 2006 reassessment of current use pesticides and to fill critical gaps and uncertainties. The effects research results will be used to support the chlorotriazine reassessment, define the risks from toxicant exposure(s) to two susceptible populations (children and pregnant women), understand the latent and/or persistent effects of developmental exposure to selected pesticides, and compare the sensitivity of the developing nervous, immune, and reproductive systems. A prototype multimedia, multipathway exposure and dose modeling approach and improved gastrointestional and dermal exposure modeling models were furnished

to OPP for assessing aggregate risks and better estimating toxicologically relevant doses. OPP was also provided an updated database of body burden measurements of pesticides and toxics that they will use in future aggregate risk assessments.

Approach for Selecting and Prioritizing Future ORD Research Activities

Following the October 2002 meeting with the OPP scientists, the ORD members of the Safe Food Research Coordination Team (ORD-RCT) employed a step-wise approach to identify, select, prioritize and plan future FQPA-related research to address OPP/OPPTS' highest priority research needs. The list of research needs had not significantly changed since the September 2001 planning meeting, facilitating the accomplishment of this process. In going from the lengthy list of OPP research priorities in Appendix 1 to a targeted set of research activities that could be addressed with the Safe Food resources, the ORD-RCT again considered relevant research being planned both within and outside EPA along with ORD's science expertise, capabilities, and capacity.

The ORD-RCT team first compared OPP's needs (Appendix 1) against the FQPA-related research needs outlined in other relevant science and guidance documents (*Strategy for Research on Environmental Risks to Children*, *Pesticides in the Diets of Infants and Children*, OPP's Policy on Determination of the Appropriate FQPA Safety Factor(s) for Use in the Tolerance-Setting Process (USEPA 1999c), etc.). This analysis yielded a more complete understanding of the overall FQPA-related research needs that were then categorized into one regulatory activity and four science driven research themes.

- Science to support the 2006 reassessment of current-use pesticides (Regulatory)
- Science to understand the critical factors influencing aggregate risks (special consideration given to children)
- Science to understand the critical factors influencing cumulative risks (special consideration given to children)
- Science to address the uncertainties associated with when to apply the 10X safety factor
- Science to support incorporation of physiologically-based pharmacokinetic models and data into risk assessment.(special consideration given to children)

The ORD-RCT then reviewed the research being planned and implemented across all the other ORD GPRA research programs. This provided insights into other ORD research programs that are sponsoring relevant research that can be used by OPP/OPPTS along with the Safe Food outputs to address the FQPA mandates. For instance, ORD develops toxicity testing methods under the Safe Communities, Human Health, and Endocrine Disrupting Compounds MYPs. ORD's fundamental modeling research (source, exposure, dose, PBPK/PD, dose response, etc.) is being planned and conducted under ORD's Sound Science research program. Research addressing drinking water issues is planned and conducted under the Clean and Safe Water MYPs. Risk management research is primarily planned and conducted under the Pollution Prevention MYP, with limited research being planned and conducted through the Safe Communities research program. Linkages with these other research programs are reflected in

Appendix 1 and highlighted in the narrative below. Relevant FQPA research being planned within other ORD GPRA research programs, as annotated in Appendix 1, was then removed from consideration for inclusion in the Safe Food FQPA research program.

The remaining high priority OPP research needs were examined in light of the existing ORD Safe Food FQPA capabilities and capacities. A corresponding series of critical science questions was then compiled to frame the future Safe Food research program:

- What are the critical factors influencing cumulative risks from pesticides with a common mode of action? (With a focus on infants and children)
  - What are the primary exposures pathways, magnitude of these exposures, and factors influencing the exposures?
  - What are the age/developmental-stage related differences in exposure and susceptibility?
  - What are the patterns of exposures (timing, frequency, and magnitude) to single and/or multiple pesticides?
  - Do these varying exposures result in an additivity of health effects?

- How can we reduce the reliance on uncertainty and safety factors in risk assessments for children under FQPA?
  - Is the 10X Safety Factor adequate or overprotective?
  - What are the mechanisms of action underlying differential responsiveness of sensitive subpopulations defined by lifestage?
  - What data and models are needed to reduce the uncertainty and better understand the variability?

- How do we improve future FQPA risk assessments?
  - What risk assessment tools are needed?
  - What are the best approaches for linking pharmacokinetic (PK) and pharmacodynamic (PD) models to produce more accurate dose-response assessments?
  - How can physiological, pharmacokinetic, and mechanism of actions data be incorporated into risks assessments?

Long-Term Goal, Annual Performance Goals, and Annual Performance Measures

The ORD-RCT, focusing on the reduced list of OPP/OPPTS research topics and activities (areas identified as Safe Food in Appendix 1), updated its current Safe Food research program and designed a future research program commensurate with available ORD resources that will produce high quality exposure, effects, risk assessment, and risk management data and tools that can be employed by OPP/OPPTS in implementing the FQPA requirements. The principles and processes outlined in the Logic Model (McLaughlin, 1999), working from right to left, were fully incorporated in this science planning activity to ensure the program delivers the right products at the right time to OPP. ORD's direct contributions within the Logic Model

framework (Figure 2) end with the Short-Term Outcomes (Change in Customer Actions). From this point forward, ORD's contributions are combined with the scientific contributions from other EPA (including OPP) and non-EPA scientific organizations to support the achievement of the overarching Intermediate and Long-Term Outcomes.

A single Long-Term Goal (LTG) [*Logic Model Short-Term Outcomes, Change in Customer Actions*] for ORD's Safe Food research program was developed:

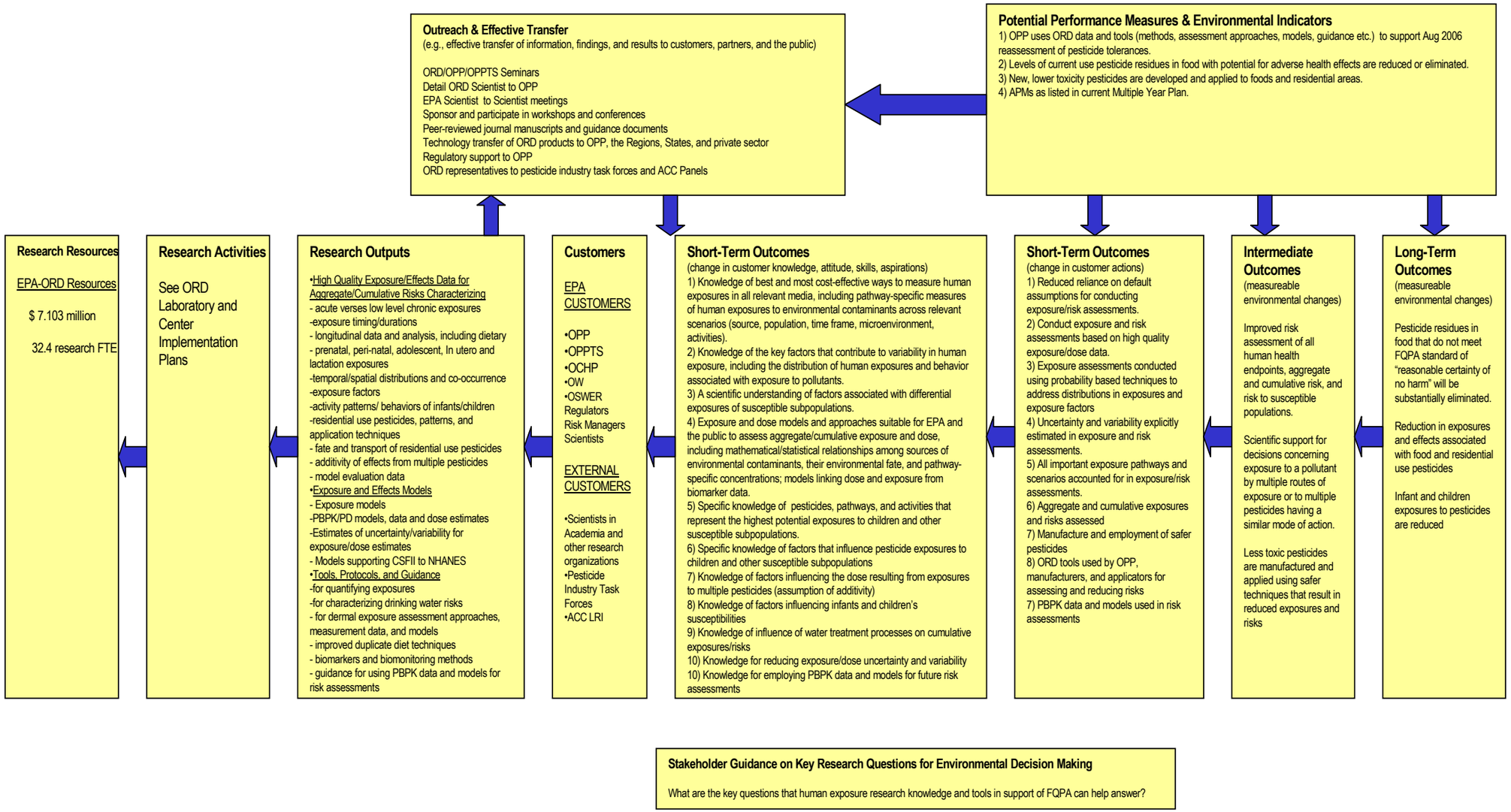
> ***By 2008, provide scientific tools to OPP/OPPTS that can be used to characterize, assess, and manage risks across the exposure-to-dose-to-effects continuum in implementing the FQPA requirements***.

The resulting Safe Food research program is organized and planned to address, in a step-wise manner, the reduced list of OPP's highest priority research issues. The research areas being addressed in this MYP have been organized within four broad research themes: aggregate risks, cumulative risks, 10X safety factor, and the use of physiologically based pharmacokinetic (PBPK) data and models in risk assessment. It is important to note that although aggregate and cumulative risk research are each addressed separately in this MYP, many scientists consider aggregate and cumulative risks as a single research area, as understanding aggregate risk is a fundamental building block to understanding cumulative risk. These two areas were separated within this MYP in an attempt to clearly define what is being planned and how ORD's future research programs are designed based on needs, resources, and the earlier lessons learned.

Starting with the envisioned FY 08 LTG outcome, a reverse planning process was employed to identify and sequence a series of critical steps (Annual Performance Goals (APGs) [*Logic Model Short-Term Outcomes - Changes in Customer Knowledge, Attitudes, Skills, or Aspirations*]) that will be needed to achieve the MYP LTG outcome. Annual Performance Measures (APMs [*Logic Model Research Outputs*]) needed to achieve the desired APG outcomes were identified and submitted to the various ORD laboratories and centers for their review and concurrence. The laboratories and centers were challenged to design research programs that would produce one or more high quality outputs that would comprise the APMs and subsequently support the accomplishment of the APG outcomes. The plans for producing these products are detailed in the ORD laboratory- and center-specific implementation plans.

Nine APGs have been identified: one addressing aggregate risks research issues, one addressing 10X safety factor research, one addressing sound science to support the 2006 reassessment, three addressing cumulative risk research, and three for using the PBPK data and modeling framework for risk assessment. The outcomes from these nine APGs contribute to the accomplishment of the FY 08 MYP LTG. Figure 3 displays the sequencing and integration of these APGs within the LTG framework and demonstrates how ORD has focused the Safe Food

• Figure 2: Program Logic for ORD's Goal 3 Safe Food Research Program



research program to address the highest priority FQPA questions. This research program builds, in an iterative fashion, upon ORD's earlier exposure-to-dose-to-effects research successes. Research addressing the four broad themes can readily be visualized along three horizontal axes: aggregate risk follows the central horizontal axis, cumulative risk is along the top axis, and PBPK data and models along the lower axis. Although the APG for the10X safety factor related research can be visualized along the central axis, it is also integrated into the other research themes. Appendix 2 lists the ORD designated APMs (FY 01-04) and proposed outyear research APMs that will support the accomplishment of the APGs.

Figure 3 illustrates how ORD, with continuous consultation with OPP/OPPTS scientists and managers, has designed a responsive Safe Food research program to address OPP/OPPTS' critical needs. The FY 03 APG represents the culmination of ORD's past research prior to the implementation of the MYP process. Science questions addressed in this earlier program include research in aggregate and cumulative risk and children's health related to the FQPA safety factor, with the majority of the existing research program targeted to address data gaps and uncertainties associated with aggregate exposure and risk. The FY 04-08 APGs were developed to address OPP/OPPTS' highest priority research needs. In FY 02, the program shifted emphasis towards cumulative risks and PBPK data and models for risk assessment. While the focus shifts, additional high priority aggregate risk questions may be uncovered through the analysis of the past on on-going aggregate risk scientific findings. These additional aggregate risk science questions will be prioritized and considered, in consultation with OPP, for future research during the future ORD/OPPTS planning meetings.

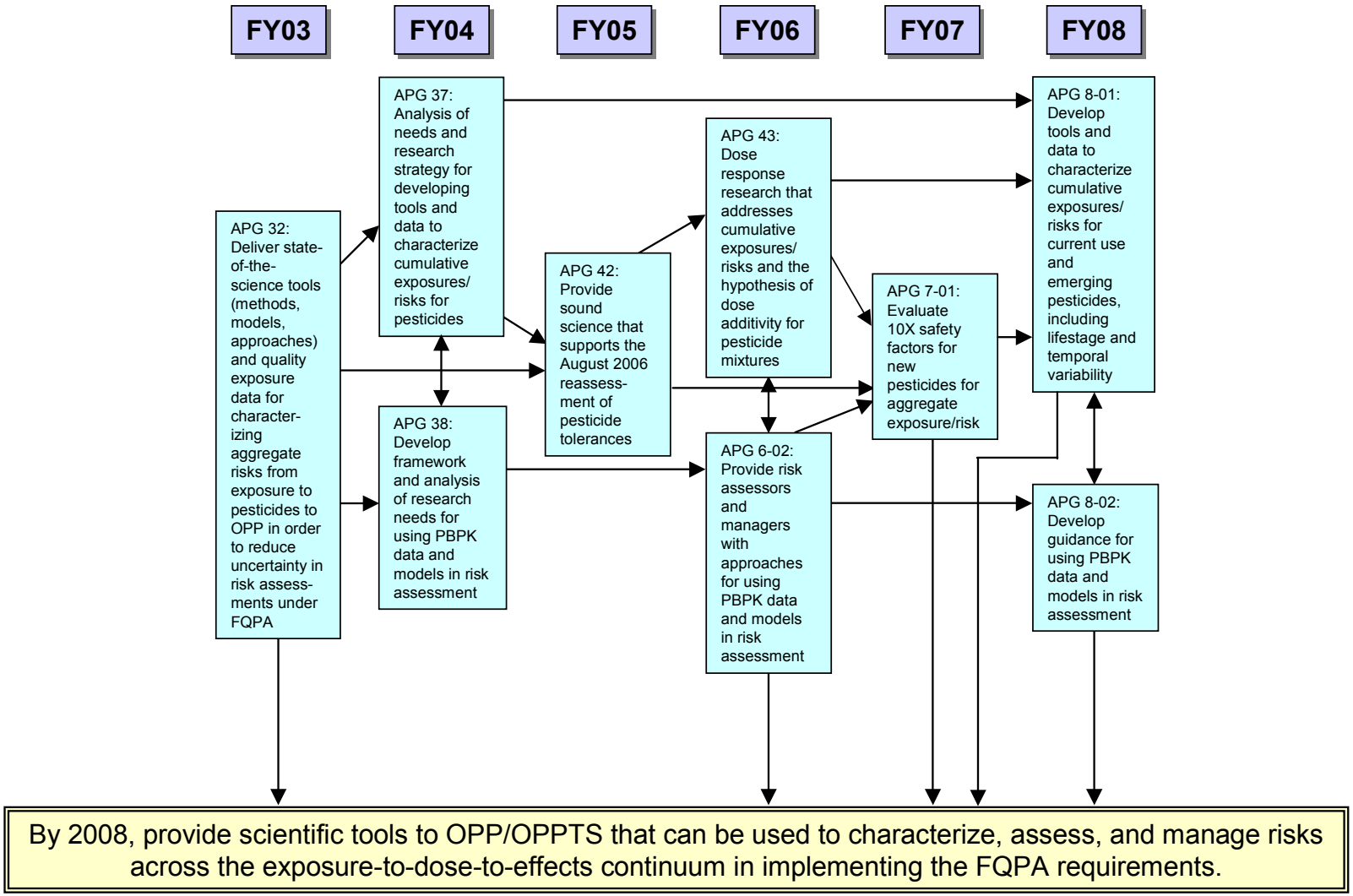
The FY 04-08 APGs build on the successes of ORD's aggregate research that was in place prior to the implementation of the MYP planning process. The MYP directed research program is designed to: 1) complete the current research addressing high priority aggregate risk research (APG 42) and 2) start shifting focus towards addressing the critical cumulative risk research issues (APG 37) and developing a framework for using PBPK data and models for risk assessment (APG 38) as described below:

a. Aggregate and cumulative exposure and risk.

Research in aggregate exposure and risk follows the central horizontal axis (APG 32, APG 42, APG 7-01, and APG 8-01). ORD's aggregate exposure and risk research serves as the foundation for the cumulative exposure and risk program, and is directly linked to all the other research topics.

The results from ORD's FY 01-05 aggregate and cumulative risk research will be provided to OPP/OPPTS no later than FY 05 to support the August 2006 pesticide tolerance reassessments.

Figure 3: Goal 3 Safe Food: Food Quality Protection Act



The FY 03 aggregate exposure and risk research focuses on completing the development of methods and protocols for measuring OP and pyrethroid pesticides and selected biomarkers. Several large-scale (e.g., CTEPP) and small targeted exposure studies are being conducted by NERL. Some of these studies are collaborative efforts with ORD's National Center for Environmental Research (NCER) sponsored Science to Achieve Results (STAR) Grants program and other Federal Agencies (HUD, CDC, etc.). These studies focused primarily on characterizing children's aggregate exposures to pesticides in daycare centers and in other residential settings. Critical factors influencing these young children's exposures are also being characterized. The results of these studies, the NHEXAS pilot studies results (Human Health MYP), and the US/Mexico Border Study results (Human Health MYP) are currently being analyzed and reported (FY 01-04). The validated aggregate exposure, exposure factor, and time activity data are being made publicly available through NERL's Human Exposure Database System (HEDS). In 2004, ORD will complete the analysis of new data on pesticide-related exposure factors collected by the STAR program, additional exposure studies sponsored by NERL, and CDC's National Health and Nutrition Examination Survey (NHANES) (CDC 2001). These exposure factor data will be incorporated into ORD's National Center for Exposure Assessment's (NCEA) Exposure Factors Handbook. Based on current studies results, an integrated protocol for measuring children's exposure to pesticides is being developed and will be peer reviewed. An exposure field study will be planned and conducted (FY 02-06) to validate this comprehensive protocol and to develop distributional data on aggregate pesticide exposures and exposure factors for children of different age groups. Results will also be used to evaluate age and developmentally related differences in exposure.

Aggregate exposure and dose models (Stochastic Human Exposure Dose Simulation (SHEDS) and Exposure Related Dose Estimating Model (ERDEM), respectively) have been developed, evaluated and refined using the early ORD real world exposure measurements data. Enhancements to these models include upgraded double Monte Carlo modeling techniques for estimating uncertainty and variability. These two models are being integrated (FY 02-04) to serve as the foundation of the exposure-to-dose-to-effects modeling framework. New dermal exposure and ingestion modeling modules are being developed and evaluated, to include associated PBPK components. Following their initial evaluation, these modules will be incorporated into the upgraded ERDEM model.

Additional analyses of the aggregate exposure and risk data will be initiated in FY 03 to determine future critical aggregate exposure and risk data gaps and research needs, along with research issues associated with understanding the potential exposure and related effects from exposures to new and emerging pesticides. Follow-on aggregate exposure and risk research activities will be conducted (FY 04-07) to address these critical data needs, and these additional research data will be provided to OPPTS by FY 08 (APG 42, APG 7-01, and APG 8-01).

ORD's research focus started shifting emphasis in FY 02 from aggregate to cumulative exposure and risk issues (upper horizontal axis in Figure 3, APG 37, APG 43, and APG 8-01). In FY 02, ORD's identified critical data gaps and research needs to meet OPP/OPPTS cumulative risk research needs. A series of data and modeling analyses and workshops will be

conducted (FY 03-04) to identify and prioritize cumulative exposure and risk research needs and to develop an ORD research strategy (APG 37) for Safe Food that will produce tools (methods, data, models) for characterizing and assessing cumulative exposure and risk (APG 8-01). A gap analysis will be conducted to identify research needs for improving assessments of cumulative exposures and risks (FY04), modeling tools and data will be developed to address these gaps (FY06-07), the tools and data will be applied to address specific Agency needs for cumulative assessments (FY06-11), and refined tools and databases will be documented (FY12).

ORD's National Health and Environmental Effects Research Laboratory (NHEERL) will sponsor several workshops to examine mechanistic issues from single pesticide and multiple pesticide exposures, and to better understand the different effects resulting from exposures to multiple pesticides with common modes of action (FY 03). ORD will also conduct research on mechanisms of action under the Human Health MYP, looking at chemicals with common modes of action and both the same and different endpoints. Effects research will also examine dosimetry issues including questions addressing dose-additivity (FY 04-06), interactions from exposures to multiple pesticides (FY 05-06), and age-related differences in response to repeated pesticide exposures (FY 05-06).

FQPA requires that drinking water be considered as a pesticide exposure pathway in human health risk assessments. This requirement has prompted the development of new tools, techniques and information, to include drinking water protocols that will evaluate treatment of pesticides in drinking water sources.

Water treatment processes are highly variable among community water systems. Preliminary data suggest conventional water treatment processes do not appear to remove most pesticides. Chemical water softening and disinfection processes, however, may cause chemical transformation of some pesticides into toxic by-products. The prediction or quantification of water treatment effects on pesticide removal and transformation is a critical aspect in understanding the impact of pesticides in drinking water on human health. Because the regulated community is responsible for generating the necessary data for pesticide risk assessments, standard testing protocols and testing strategies for evaluation of water treatment effects on pesticide removal and transformation need to be developed and provided to pesticide manufacturers.

ORD's National Risk Management Research Laboratory (NRMRL) will conduct research address the pesticides in drinking water science issues. Risk management related research starts in FY 03 and continues through FY 08 with the development of drinking water protocols that will be utilized by the pesticide manufacturers in assessing risks from treatment effects on pesticides in drinking water sources. The first phase of the protocol will be completed in FY 05 (APG 8-01) with an updated protocol being developed in FY 08. The updated protocol will be defined by an expansion of the original protocol to include a broader range of parameters such as, additional treatment processes, increased water production, and additional water sources. Additional drinking water is being conducted within the Safe Communities MYP. Additional, risk management research will be based on current and future OPP/OPPTS needs.

By FY 08, ORD will provide a refined set of modeling tools for assessing aggregate exposures and cumulative risks from pesticide exposures. These tools will include a suite of modules for characterizing sources, human exposures, and resulting dose, as well as the computational links to facilitate efficient application of the modules to address specific Agency needs. Validated exposure databases from ORD's field exposure studies will also be readily available. The state-of-the-art models will be applied to OPP assessments conducted to meet their pesticide registration requirements. The Safe Food research program will also contribute to the Agency's guidance being developed through the Risk Assessment Forum for aggregate and cumulative risk assessment under Human Health.

However, ORD recognizes and anticipates that at the end of this planning cycle (FY 08), major uncertainties regarding aggregate/cumulative risks from exposures to pesticides will likely remain. ORD's current approach is based on a number of default assumptions reflecting the Agency's current understanding of exposure and dose additivity. Over this planning cycle, ORD's exposure research will likely uncover new issues regarding key factors influencing children's exposures to pesticides. The effects methods under development assume that the dose response and dose additivity relationship is the same across species, endpoints, life stages and exposure paradigms (i.e. episodic vs. continuous low dose). These initial cumulative risk models are thought to provide estimates of risk within an order of magnitude. In order to provide more accurate estimates of risk, a better understanding of the influence of mode-of-action and pharmacokinetics on the choice of models is required.

b. PBPK Modeling. OPP has identified research to improve use of biological data, including pharmacokinetic data, in risk assessments as one of its highest priorities. One way to incorporate biological data into risk assessments is through the use of PBPK models. PBPK models address the exposure-dose relationship in an organism taken as a whole, estimating the dose to a target tissue or organ by taking into account rates of absorption into the body, metabolism, distribution among target organs and tissues, storage, and elimination. PBPK models are useful in extrapolating between animals and humans and between children and adults because they allow consideration of species- and age-specific data on physiological factors that affect dose levels and data on biological responses that are different or more intense in certain subpopulations such as children. PBPK models also have applications related to assessment of cumulative risk and extrapolation between routes and provide mechanistic links between exposures and doses. NCEA, NCER, NERL, and NHEERL are all supporting research and risk assessments using PBPK models. Drawing upon its considerable expertise and experience in this area and through collaboration with OPPTS, ORD will provide approaches and guidance for using PBPK data and models in future risk assessment that will integrate the results of ORD's research and provide new methods, models, and data for risk assessments of pesticides and other toxic chemicals. This research follows the lower horizontal axis in Figure 3 (APG 38, APG 6-

02, APG 8-02). The first step (APG 38) will be to complete an approach as a foundation for comprehensive guidance.

The framework and guidance will draw upon research results of the ORD intramural and

STAR programs. The NERL exposure work described above for aggregate and cumulative risk, particularly that relating to the SHEDS and ERDEM and their related data collection activities, will be major contributors to the development of this PBPK-based risk assessment guidance. The PBPK guidance and related data and models, in turn, will be a part of the set of guidance documents developed for aggregate and cumulative risk and will contribute to the source-to-exposure-to-dose-to-effects model described above. Related NHEERL and NCEA research outlined in the Human Health MYP will identify key parameters for PK/PD models for interspecies extrapolation and provide information on the use of pharmacokinetic data in risk assessments for children. The STAR program will provide research results for using PK data to interpret biomarkers. Contributions will be sought from experts through workshops held to delineate issues and to provide a peer review of program outputs. The guidance will provide: analysis and recommendations for use of PBPK data and models in risk assessment; analysis of relevant issues such as age-related dosimetry and extrapolation between species, age groups, and exposure routes; databases of factors for test animals and humans, such as blood flow rates, organ weights, and parameters describing metabolism; and more realistic risk assessment methods that reduce the use of default assumptions.

c. FQPA Safety Factor for Children. Much of the study of aggregate and cumulative risk and the related topic of PBPK modeling involves studies of children's issues. The Safe Food research results will assist OPP by: providing critical data to fill data gaps and reducing the risk assessor's reliance on the use of default assumptions; developing improved risk assessment methods, approaches, and protocols for children; assessing the need for application of the safety factor on a case-by-case basis; and informing the risk assessors so that they can refine the science policy on the safety factor. APG 7-01 reflects the goal of evaluating the safety factor in light of anticipated research results from the Safe Food research program.

Research Focus for FY 2008 to FY 2012

ORD's Safe Food research program, as outlined in this MYP, will clearly not address all of OPP's highest priority children's risk and aggregate/cumulative research needs by FY 08. And as noted above, new science issues will likely be uncovered as ORD conducts its research activities that will need to be addressed as ORD continues to plan and conduct research in this area. So it's important to start the process of outlining potential research areas for consideration after FY 08, recognizing that this is not a complete list of potential research areas.

Once the currently planned research program is completed, ORD's cumulative risk research program will likely be focused on identifying the underlying, default assumptions used in these methods and models and test their validity. These initial exposure and effects models will be refined using a few select pesticides with known modes-of-action. It is likely that the mode of action of different classes of pesticides will require slightly different approaches and that the default assumptions used in these models may not apply to all modes-of-action. It will also be important to understand the influence of mode-of-action and pharmacokinetics on these default assumptions.

A number of pesticides induce toxicity through alterations in physiological signaling pathways. These pathways are normally under homeostatic controls. It is likely that altering these signaling pathways through different mechanisms results in a diverse response at different biological levels to maintain homeostasis. These homeostatic responses may influence cumulative risk models depending on whether they were based on acute vs. chronic toxicity data. In addition, the types and magnitude of these homeostatic responses are likely to be dependent upon the life stage studied.

In the approaches taken for aggregate/cumulative risks and efforts to address the 10X safety factor, information on mode-of -action and pharmacokinetics are critical. The 10X safety factor was proposed because it is believed that there are pharmacodynamic and toxicokinetic differences in response to chemicals at different life stages. Thus providing quantitative methods and data to incorporate mode-of-action and pharmacokinetic information into these models will allow for the replacement or refinement of the default assumptions used in the aggregate and cumulative risk models and in the 10X safety factor.

By FY 12, ORD's research is anticipated to be designed to assess the impact of modes of action (MOA) on the ability of these models to predict cumulative risk. Investigations will likely focus on one or more classes of chemicals with varied MOAs. These research efforts will include identifying the default assumptions in these models and will develop into a research program to test those assumptions. In addition, these efforts will focus on how mode of action and pharmacokinetics affect those assumptions. If we understand how MOA and pharmacokinetic parameters influence these assumptions we will be able to define in more detail the types of information needed to develop more predictive models. Furthermore, understanding MOA provides scientific basis for developing quantitative descriptions between different life stages and species which will allow us to refine the 10X factor.

Research that Would Close Critical OPP Science Gaps With Additional Resources

The Food Quality Protection Act raises more high priority scientific issues than can be addressed by EPA within the Safe Food research program at any given time. As with any program, OPP's research needs for implementation of FQPA outpace the resources available. Thus, priorities need to be established about the research to be conducted by ORD.

This section describes four key research areas that ORD would focus its efforts to support OPP's implementation of the FQPA if there were an additional twenty percent increase in resources over a consecutive three to five year period (not in order of priority): Aggregate risk,

analytical chemistry, toxicity screening tests and alternatives to animal models, and the application of computational toxicology tools and methods for solving complex science issues.

<u>Aggregate Risk</u>

EPA has chosen to focus its FY 03 and beyond research efforts to help OPP implement

FQPA on some of the key uncertainties surrounding the application of the 10X safety factor, the assessment of cumulative risk and the use of physiologically based pharmacokinetics to refine risk assessment models. Although aggregate risk was the primary focus of the early Safe Food research program, ORD has started shifting its research emphasis from aggregate risk to addressing other high priority FQPA research needs. Thus, the first area of focus for the application of additional resources would be on aggregate risk to strengthen and validate the requirement for a 10x safety factor for infants and children. When increased exposure in children can be identified, ORD will conduct studies to address key exposure and effects issues including the biology needed to establish whether there is an increased risk.

OPP rarely gets information to assess pesticide exposure from more than one route. Therefore assumptions have to be made about the aggregate exposure and risk. Effective assessments of aggregate exposure require that OPP measure the level of exposure to the pesticides of concern, model these exposures, assess whether there are differences in uptake or target organ dose between the young animals and adults and to identify the key routes of exposure and uptake. The following research could provide additional information about aggregate exposures and reduce the uncertainties in assessing aggregate risk.

a. Conduct Exposure Measurement Research. Additional research would be performed to determine which residential factors have the greatest impact on children's pesticide exposure and to develop criteria for identifying sub-populations that are highly exposed to residential-use pesticides. Targeted research studies include: (1) pesticide use patterns, (2) impact of pesticide application practices, scenarios, and formulation on residential exposure, (3) impact of demographic and housing factors on children's exposure to residential-use pesticides, and (4) classifying children's activities and behaviors to characterize aggregate exposure.

b. Exposure Modeling Research. Research would be performed to develop new methods and standardized protocols for collecting micro-activity data (e.g., mouthing behaviors), better characterize intra- and inter-individual variability of micro-activities within a macro-activity context, and develop/evaluate approaches for characterizing and modeling indirect ingestion exposures.

c. Assess whether there are differences in uptake or target organ dose between young animals and adults. The initial focus would be to conduct developmental neurotoxicity testing of selected triazole pesticides.

d. Conduct dietary research to better understand the key routes of exposure and uptake. Research would be performed to develop analytical and field exposure methods and investigate the levels of pesticide metabolites present in foods prior to consumption to improve the interpretation of biomarker data.

e. Extend the aggregate exposure assessments in adult rats to young rats using carbamate pesticides and possibly other classes of pesticides.

f. Multi-route dosimetry and PBPK modeling. Research would be performed to develop and enhance dosimetry models for the inhalation, oral, and dermal pathways, to improve methods for performing aggregate and cumulative risk assessments.

Testing Screens and Alternative Testing Models To Reduce The Number of Animals

Several factors drive OPP's needs for the development of testing screens and alternative test methods and protocols to those now in use. Some key driving factors include: that the current tests take too long; they are too expensive; they use too many animals; and they are not sufficiently predictive. Additional work on the development of new screens, assays, and models would build on and bring together the three focus areas of the current ORD work to be conducted under this MYP until FY 2008 (i.e. aggregate risk, cumulative risk and PBPK).

To ensure that our next steps will provide OPP with the tools and methods they need for the future, workshops between ORD and OPP staff could be conducted and a series of white papers developed to identify which research area(s) will likely provide the biggest payoffs and which are likely possible lines for fruitful research. Through these interactions the tests that are most animal intensive, least predictive, most expensive or time consuming, etc., can be identified. In addition, areas could possibly be identified in which in vitro assays could play a role in refining or reducing animal use. Ongoing discussions with OPP will be critical to determine what criteria need to be met before they can use alternative and/or screening tests to regulate pesticides. The Science Advisory Panel and other advisory groups will likely need to be consulted about how best to proceed. These key areas are where additional resources could be applied if they were to become available:

a. New predictive, reliable and rapid toxicity testing methods and protocols are needed to make the pesticide registration process more efficient and predictive and to reduce the number of animals that need to be sacrificed during the pesticide registration process. Efforts would be made to link this program with ORD's computational toxicology research program (see below). Initial and ongoing dialog between ORD and OPP will focus the efforts on OPP's vision about how they envision using the methods for risk assessment.

b. Develop new methods and protocols for determining mechanism of action and to assess effects of mixtures of pesticides with a focus on developing new *in vitro* assays to replace *in vivo* assays.

c. Conduct workshops between ORD and OPP staff to identify which research areas will likely provide the biggest payoffs and which are likely possible lines for fruitful research

Analytical Chemistry

Upon close inspection, areas can be identified where additional analytical chemistry could provide OPP with needed information for making risk assessment decisions. For example, a lack of sufficiently sensitive, reliable and accurate analytical chemistry data and methods are a

stumbling block to the identification of potentially toxic breakdown products and the levels of the products both in the environment and in target organs that lead to unreasonable exposures. Further, the lack of sufficiently sensitive analytical chemistry methods, ones that could be based on advances in nanotechnology and miniaturization, thwarts PBPK studies. In both cases, assumptions must be made, resulting in increased uncertainty in the final assessments.

If additional resources were to become available, an additional focus in this area would be to investigate the impact drinking water treatment may have on pesticides. It is suspected that some water treatment processes may be altering pesticides and in the process producing potentially toxic pesticide byproducts. These byproducts need to be identified and quantified so that assessments can be made as to their toxic potential and additional research needs identified. Close coordination between ORD, OPP and the Office of Water (OW) will be needed to successfully plan and conduct this work to generate products that the Program Offices, Regions, States, and municipalities can employ to protect human health.

Application of Computational Toxicology Tools and Methods

Significant efforts are underway within ORD to develop computational toxicology methods to better assess environmental risks. Some of these computational toxicology approaches are likely to be available starting in FY 06 for specific applications including tailoring into tests for pesticide registration. Many possibilities exist, and it will be critical that we ensure that our next steps will provide OPP with the tools and methods they need for the future. Workshops between ORD and OPP staff need to be conducted to determine OPP's computational toxicology related needs (e.g., where should the focus be, developing high throughput tests, predictive methods, etc.), and a series of white papers could be developed to identify which research areas will likely provide the biggest payoffs and which are likely possible lines for fruitful research.

Transferring the Skills, Tools, and Knowledge to OPP/OPPTS, the Regions, and the Scientific Community

The ORD and OPP/OPPTS senior managers and scientists have established a process for developing a "collaborative" Safe Food research, where OPP is a full partner in planning and implementing the research. This is in lieu of the more traditional "client-based" research program where OPP would only state their needs and not be engaged in the planning and conduct of the the research. While the majority of the Safe Food MYP research is being performed by the ORD scientists, OPP/OPPTS scientists now participate in the design and proposed approach(es) for conducting this research to ensure that the outputs address key OPPTS needs and produce the desired outcomes. In some instances, OPP staff participate fully as a science team members throughout the entire research program. As an example, OPP scientists are working collaboratively with ORD scientists on a competitively awarded pyrethroid research program. This "collaborative" approach for conducting research was requested by OPP in 2001 and immediately implemented by the ORD-RCT to help develop integrated research programs that would ultimately transfer the skills, tools, and knowledge to

OPP that will be used to address the FQPA mandates. In another example, ORD has established a work group that includes a member from OPP to develop approaches for using PBPK data and models in risk assessments conducted under FQPA.

In addition, the ORD-RCT has implemented several other outreach programs to facilitate the planning and transfer of research to OPPTS, the Regions, and the scientific community. The annual planning meeting and ORD/OPPTS program reviews are designed to communicate research needs and accomplishments to senior OPPTS and Regional managers and scientists. ORD has implemented a series of bi-weekly scientist seminars, with sessions rotated among the various ORD laboratories and centers. These seminars are designed to communicate our research directly to the OPPTS and Regional scientists we support. These meetings provide the OPPTS and Regional scientists with in-depth details of ORD's science programs and corresponding results. They provide an open-door opportunity for individual OPPTS and Regional scientists to provide input into the study design, conduct, and interpretation of results. ORD also plans and conducts a variety of scientist-to-scientist meetings to address emerging issues. A recent scientist-to-scientist meeting was held in Washington, DC in November 2002 to identify and address research needs for using PBPK data and models in future risk assessments. The ORD laboratories and centers also schedule other workshops and meetings with selected OPPTS and Regional representatives to address specific organizational issues. For instance, NERL exposure modelers sponsored a workshop to examine the strengths of the four aggregate exposure models being sponsored by OPP/Health Effects Division.

Key research results (APMs) and other significant ORD products are delivered to OPPTS and the Regions by the respective ORD laboratory and/or center. Follow-ups are then made by the corresponding ORD leads for the research (OSP and laboratory/center representatives) to ensure that OPP understands and is using the new science. ORD provides the Safe Food results to the scientific community through peer reviewed publications.

Linkages to Other Research Programs

This Safe Food research program builds upon the research and technical support sponsored by other ORD research programs (Appendix 1) and by other Federal Agencies and non-governmental organizations, both in the US and throughout the international scientific community.

Other ORD Programs. This MYP employs many of the fundamental sound science tools developed and evaluated under ORD's Human Health MYP and the science outlined in ORD's draft *Human Health Research Strategy* as well as ORD's *Strategy for Research on Environmental Risks to Children*. Some of the core research programs being conducted under the Human Health Susceptible Subpopulations and Aggregate/Cumulative Risks research programs serve as the foundation for, or are directly integrated into, the Safe Food program. In these instances, the Human Health outputs are modified to address specific Safe Food pesticide specific issues. The alignment of Safe Food and Human Health research is required to bring sufficient resources to address the FQPA-related science issues. The Safe Food research also

parallels some of the human exposure-to-dose-to-effects research being planned and conducted under ORD's Safe Communities and Emerging Risks: Endocrine Disrupting Compounds research programs.

Summary of Non-EPA Research. Several Federal Agencies conduct FQPA-related research that provides scientific support to inform OPPTS decision making. Related research is also on-going throughout academia and other non-governmental organizations.

The National Institute of Environmental Health Sciences (NIEHS) achieves its mission through multi-disciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach.

For example, the NIEHS program includes a trans-National Institutes for Health effort to study effects of chemicals, including pesticides and other toxics, in children. EPA has collaborated with NIEHS in establishing Centers for Children's Environmental Health and Disease Prevention to define the environmental influences, including pesticides, on asthma and other respiratory diseases, childhood learning, and growth and development. NIEHS and the National Institute of Allergy and Infectious Diseases (NIAID) are conducting the Inner-City Asthma Study, which is a prevention trial to develop an intervention strategy to reduce asthma morbidity in inner-city children and adolescents. The National Allergen Study, being conducted by NIEHS in collaboration with the Department of Housing and Urban Development (HUD), examines the relationship between allergens and lead and how allergen exposures differ as a function of geographic region, socioeconomic status, housing type, and ethnicity. NIEHS and the National Toxicology Program (NTP) develop new technologies for high-throughput toxicity testing, and these agencies are responsible for one-third of all toxicity testing performed worldwide. Long-term collaborative efforts with NTP, particularly in the areas of carcinogenesis, reproductive/developmental toxicity, and neurotoxicity, are well established. NIEHS has established the National Center for Toxicogenomics (NCT) to coordinate an international research effort to develop the field of toxicogenomics. The NCT will provide a unified strategy, a public database, and develop the informatics infrastructure to promote the development of the field of toxicogenomics. NIEHS will pay special attention to toxicogenomics as applied to the prevention of environmentally-related diseases.

The National Cancer Institute (NCI) conducts population-based research on environmental and genetic causes of cancer and on the role of biological, chemical, and physical agents in the initiation, promotion, or inhibition of cancer and the biological and health effects of exposure to radiation. NCI is the leading Federal Agency planning and conducting a prospective study of agricultural pesticide applicators and their family through the interagency Agricultural Health Study. NERL is conducting an exposure study (FY 00-02) in support of this NCI sponsored study (Safe Communities).

The Centers for Disease Control and Prevention (CDC), through the National Center for Environmental Health (NCEH), studies health problems associated with human exposure to lead,

radiation, air pollution, and other toxicants, as well as to hazards resulting from technologic or natural disasters. These are mainly surveillance and epidemiology studies. NCEH is particularly interested in studies that benefit children, the elderly, and persons with disabilities. The National Center for Health Statistics (NCHS) of CDC is conducting the National Health and Nutrition Examination Survey (NHANES)-4. NHANES-4 is a national population-based survey and includes data on potentially sensitive subpopulations such as children and the elderly. EPA is participating in this survey with NCHS to collect information on children's exposure to pesticides and other environmental contaminants. CDC's *National Report on Human Exposure to Environmental Chemicals* is a new publication that provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring data collected through NHANES. The first report provides information about biomonitoring levels of 27 chemicals, including many pesticides.

The National Institute of Child Health and Human Development (NICHD) supports laboratory, clinical, and epidemiological research on the reproductive, neurobiological, developmental, and behavioral processes that determine and maintain the health of children and adults. ORD is collaborating with NICHD, CDC, and other Federal agencies in the design and implementation of the National Children's Study (NCS) of 100,000 children, who will be enrolled during the mother's pregnancy and followed throughout childhood and adolescence. This study was mandated in the Children's Health Act of 2000 to study environmental influences on children's health and development. The relationship between pesticides exposure and adverse health outcomes will be included in this study.

The National Center for Toxicological Research (NCTR) supports fundamental research on the effects of chemicals regulated by the Food and Drug Administration. Although some of the models used by NCTR may be similar to those used by EPA, the chemicals and regulatory context vary significantly. Historically, NCTR has been a leader in developing models and principles for risk assessment, which has led to collaborations between EPA and NCTR scientists.

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Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
Effects of Pesticides with Common Modes of Action		
• Investigate assumption of additivity in assessing pesticides with common modes of action (e.g., mixtures of organophosphates, mixtures of pyrethroids, etc.)	Framework to identify and assess common modes of action for pesticides (NCEA) *Framework for use of mechanistic data in risk assessment (NCEA)* *Cumulative risk assessment methods & guidance (NCEA)* *Fundamental research on interactions between mixtures of organophosphates and organophosphates and pyrethroids to address principle of additivity (NHEERL)* *Examination of mechanisms of developmental toxicity an susceptibility with research focused on the mode of action of the developmental toxicity of perfluorooctane sulfonate (PFOS) (NHEERL)* Biomarkers research for pesticides (NCER) Use of Mechanistic Data in Risk Assessment (NCER)	Safe Food Human Health Quality Environmental Information, Human Health Human Health Safe Communities Safe Food Human Health
• brief (1-2 day) vs. continuous exposures and improved understanding of corresponding effects	Framework to identify and assess common modes of action for pesticides (NCEA) *Framework for use of mechanistic data in risk assessment (NCEA)* *Cumulative risk assessment methods & guidance (NCEA)* Children's exposure measurement studies (NERL, NCER) Longitudinal Pesticide Exposure Studies (NCER) Children's activity patterns/videotaping (NERL) *Fundamental research on effects of short-term versus long-term exposure to chlorpyrifos (NHEERL)*	Safe Food Human Health Quality Environmental Information, Human Health Safe Food, Human Health, Emerging Risks, EDCs Safe Food Safe Food, Human Health, Emerging Risks, EDCs Human Health

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
• linking exposure timing/duration to timing/extent of effects	Framework to identify and assess common modes of action for pesticides (NCEA) *Framework for use of mechanistic data in risk assessment (NCEA)* *Cumulative risk assessment methods & guidance (NCEA)* Linking temporal exposure/effects study periods (NERL, NHEERL)	Safe Food Human Health Quality Environmental Information, Human Health Safe Food, Human Health
• longitudinal data and analysis	Framework to identify and assess common modes of action for pesticides (NCEA) *Framework for use of mechanistic data in risk assessment (NCEA)* *Cumulative risk assessment methods & guidance (NCEA)* Children's exposure measurement studies (NERL, NCER) Children's time activity patterns/videotaping (NERL) NHEXAS, CTEPP, STAR Grant data analysis (NERL, NCEA, NCER) Longitudinal Pesticide Exposure Studies (NCER)	Safe Food Human Health Quality Environmental Information, Human Health Safe Food, Human Health, Emerging Risks, EDCs Safe Food, Human Health, Emerging Risks, EDCs Safe Food, Human Health, Emerging Risks, EDCs Safe Food
• consistent exposure/effects study times for cumulative risk studies	Linking temporal exposure/effects study periods. (NERL, NHEERL, NCEA) *Methodologies for the evaluation of health endpoints (immunologic, neurologic, and developmental) and exposure assessment in children are being developed and evaluated (NHEERL)*	Safe Food, Safe Communities, Human Health Safe Communities

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
Toxicity Testing and Methods		
• tests to assess mode of action	Basic research on mode of action of pesticides and endocrine disruptors (NHEERL) *Examination of mechanisms of developmental toxicity and susceptibility with research focused on the mode of action of the developmental toxicity of perfluorooctane sulfonate (PFOS) (NHEERL)* Toxicogenomic methods research (NCER)	Safe Communities, Human Health Safe Communities Safe Food, Human Health
• new tiered approach with more screening assays	*Contribute to development of a new testing paradigm through the development of new tests or refinement of new tests (NHEERL)* *Development of QSAR/SAR approaches (NHEERL)*	Safe Communities Safe Communities
• evaluate current testing guidelines to determine effectiveness of current test protocols in assessing risk and impacts of gaps in testing of endpoints – developmental immunotoxicity – developmental neurotoxicity – developmental effects in function/ organ systems not currently tested	*Fundamental research on basic biological processes in to identify specific endpoints for methodological development for testing guidelines (NHEERL)* *The particular vulnerability of the immature immune system (children) to the development of food allergies from genetically modified crops will be explored (NHEERL)* *Refinement of developmental neurotoxicological screening battery (NHEERL)* *Research to identify sensitive stages of gonad and gamete development (NHEERL)*	Human Health Safe Communities Safe Communities Safe Communities

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
• test methods for additional endpoints	*Fundamental research in support of testing for developmental exposure and subsequent carcinogenesis (NHEERL)* *Develop animal model to determine the relative allergenicity of proteins from genetically modified crops (NHEERL)* *Investigation of reproductive effects of compounds with an emphasis on genomic analysis of testicular toxicity (NHEERL)* *Development and application of more sensitive and specific endpoints (including genomic analyses) to characterize reproductive effects of pesticides and toxic substances in animal and human studies (NHEERL)* Biomarkers methods of exposure for pesticides (NERL, NCER) Toxicogenomic Methods for Pesticides (NCER)	Human Health Safe Communities Safe Communities Safe Communities Safe Food, Human Health Safe Food, Human Health
• latent effects (EDCs)	*Research to identify critical windows of vulnerability for latent effects (NHEERL)* *Research to determine the nature of latent effects later in life following development exposure to pesticides (NHEERL)*	Safe Communities, Human Health, Emerging Risks, EDCs Safe Communities
• prenatal, peri-natal, and adolescent effects studies linked with exposures	*Basic research comparing effects of exposure to pesticides at different periods of development (NHEERL)* Epidemiologic studies of children in agricultural communities investigating the link between pre and post-natal pesticide exposures and health effects (NCER) Epidemiologic studies of children in urban communities investigating the link between pre/post-natal toxic exposures and health effects (NCER)	Safe Communities, Human Health Human Health Human Health
• in utero and lactation exposures/effects	*Basic research comparing effects of exposure to pesticides at different periods of development (NHEERL)* *The elucidation of the maternal and developmental toxicity of perfluorooctane sulfonate (PFOS) in experimental animals (NHEERL)* In utero exposures of children to pesticides and other toxic chemicals in both urban and rural communities	Safe Communities Safe Communities Human Health

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
• expanded evaluations (> gross organ)	None planned	Safe Communities
• understanding pharmacokinetics in young and adult animals	*Fundamental research to develop basic biological data in support of pharmacokinetic modeling for young and adult animals (NHEERL)* Studies to develop biomarkers for use in the assessment of children's exposure and risk (NCER)	Safe Communities, Human Health Safe Food, Human Health
Exposure Modeling and Model Evaluation		
• Exposure modeling	*SHEDS/ERDEM model development and evaluation (NERL)* SHEDS-pesticides (NERL) *SHEDS- particulate matter and air toxics (NERL)* Predictive methods for pesticide dermal permeability coefficients (NERL, NCEA)	Human Health Safe Food Clean Air Safe Food, Waste, Human Health
• Spray drift modeling	None planned	Safe Communities
• targeted laboratory and field studies to obtain model evaluation data	Children's aggregate exposures to pesticides (NERL, NCEA, NCER)	Safe Food, Human Health, Emerging Risks, EDCs
Residential Exposures and Exposure Factors		
• tools for quantifying exposures	Analysis of exposure factors for pesticides (NCEA) Exposure measurements methods and protocols (NERL) Biomarker methods (NERL, NHEERL, NCER) Source-to-concentration-to-dose models/framework	Safe Food, Human Health Safe Food, Human Health Safe Food, Human Health Safe Food, Human Health
• temporal/spatial distributions of exposure and exposure factors	Analysis of exposure factors for pesticides (NCEA) Pesticides in breast milk (NCEA) Children's exposure measurement studies (NERL, NCER)	Safe Food, Human Health Safe Food, Human Health Safe Food, Human Health, Emerging Risks, EDCs

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
• activity patterns and behavior (especially infants and children)	Analysis of exposure factors for pesticides (NCEA, NERL) Children's exposure measurement studies (NERL, NCER) Children's activity patterns/videotaping (NERL, NCER)	Safe Food, Human Health Safe Food, Human Health Safe Food, Human Health
• micro/macro activities and guidelines	Analysis of exposure factors for pesticides (NCEA) Studies examining exposure estimates based on microactivity vs macroactivity data (NERL)	Safe Food, Human Health Safe Food, Human Health
• residential use, application techniques, and exposure distributions	Analysis of exposure factors for pesticides (NCEA, NERL) Children's exposure measurement studies (NERL, NCER)	Safe Food, Human Health Safe Food, Human Health, Emerging Risks, EDCs
• co-occurrence of pesticides	Pesticides in breast milk (NCEA) Children's exposure measurement studies (NERL, NCER) *Dose response studies of mixtures (NHEERL)*	Safe Food, Human Health Safe Food, Human Health Safe Communities
• dermal exposure for children	Analysis of exposure factors for pesticides (NCEA, NERL) Dermal methods and model development (NERL)	Safe Food, Human Health Safe Food, Human Health
• controls for mitigating or eliminating exposures	Studies to reduce the exposure of children to OP and other selected pesticides in agricultural communities (NCER, NERL)	Safe Food, Safe Communities, Pollution Prevention
Dietary Exposure		
• models supporting CSFII to NHANES	*Dietary models supporting conversion from CSFII to NHANES (NCER, NERL)*	*Human Health*
• longitudinal dietary exposures; impact of estimating of chronic exposures from shorter term data for the food pathway	Analysis of exposure factors for pesticides (NCEA, NERL) Targeted studies to examine critical factors influencing dietary exposures and distributions of exposure (NERL) Analytical methods to support dietary exposure estimates (NERL)	Safe Food, Human Health Safe Food Safe Food
• duplicate diet techniques	Alternative methods for duplicate diet (NERL)	Safe Food

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
Drinking Water Exposure		
• drinking water treatment: disinfection by-products, degradation products toxicity and exposure (persistence, fate, transport)	Protocols for assessing cumulative risks	Safe Food Clean and Safe Water Pollution Prevention
• ground water models/data	NA	Clean and Safe Water, Safe Communities, Ecosystem Protection
• field scale and watershed models	Probabililistic ecological modeling (PRZM, EXAM, BASS) NCER grants on water and watersheds	Safe Communities and Ecosystem Protection Ecosystem Protection
Exposure-Dose-Response Assessment		
• biomarkers and biomonitoring	Biomarker methods for pesticides exposure (NERL, NCER) *Biomarker methods for effects associated with pesticides exposure (NHEERL)* Children's exposure measurement studies (NERL, NCER) PBPK/PD modeling (NHEERL, NERL, NCEA)	Safe Food, Human Health Safe Communities, Human Health Safe Food, Human Health, Emerging Risks, EDCs Safe Food, Safe Communities, Human Health

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
• PBPK/data generation, dose estimation, and guidance	Framework and guidance for using PBPK data and models in risk assessment (NCEA) SHEDS/ERDEM (NERL) PBPK/PD models (NHEERL, NERL, NCEA) *Dose response models (NHEERL)* Pharmacokinetic studies for the assessing the effects of aggregate and cumulative exposures to pesticides (NCER)	Safe Food Safe Food, Human Health Safe Food, Safe Communities, Human Health Safe Communities, Human Health Safe Food
• dose models	SHEDS/ERDEM (NERL) PBPK/PD models (NHEERL, NERL) *Dose response models (NHEERL)* Framework and guidance for using PBPK data and models in risk assessment (NCEA)	Safe Food, Human Health Safe Food, Safe Communities, Human Health Safe Communities, Human Health Safe Food, Human Health
• route-to-route extrapolation and guidance	*In vivo and in vitro effects research (NHEERL)* Framework and guidance for using PBPK data and models in risk assessment (NCEA) Pharmacokinetic studies for the assessing the effects of aggregate and cumulative exposures to pesticides (NCER)	Safe Communities, Human Health, Emerging Risks, EDCs Safe Food, Human Health Safe Food

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
• animal-to-human dose extrapolation, e.g., dermal	*In vivo and in vitro effects research (NHEERL)* Framework and guidance for using PBPK data and models in risk assessment (NCEA) Pharmacokinetic studies for the assessing the effects of aggregate and cumulative exposures to pesticides (NCER)	Safe Communities, Human Health, Emerging Risks, EDCs Safe Food, Human Health Safe Food
• dose-response models (e.g., benchmark approaches; new approaches to RfDs)	*New approaches to RfD (RAF)* (NCEA, NHEERL, NCER) *Systematic comparisons of the dose-response and time-course of pesticide neurotoxic effects in rats of different ages (NHEERL)* *Harmonization of cancer and non-cancer endpoints (NHEERL, NCEA, NCER)*	Quality Environmental Information Safe Communities, Human Health Human Health
• probabilistic RfDs	*Harmonization of cancer and non-cancer endpoints (NHEERL, NCEA, NCER)*	Human Health
• low-to-high dose extrapolation	Framework and guidance for using PBPK data and models in risk assessment (NCEA) *Dose response modeling and extrapolation (NHEERL)* Pharmacokinetic studies for the assessing the effects of aggregate and cumulative exposures to pesticides (NCER)	Safe Food, Human Health Safe Communities, Human Health Safe Food
• quantification of uncertainty and variability (2-dimensional Monte Carlo) for exposure and dose-response	SHEDS/ERDEM (NERL) *Dose response modeling (NHEERL)*	Safe Food, Human Health Safe Communities, Human Health

Appendix 1. Crosswalk of Program Office Needs With ORD Research		
OPP/OPPTS PROGRAMMATIC NEEDS	**PLANNED ORD RESEARCH (Safe Food and Other MYPs)**	**APPLICABLE MYP**
Epidemiology Studies		
• relationship between exposure to pesticides and adverse health outcomes studies in human populations	*Agricultural Health Study* *National Children's Study* *Children's Asthma Studies* *EPA/NIEHS Centers for Children's* environmental health and disease prevention research (NCER)	Safe Communities Human Health Human Health Human Health

Appendix 2. Safe Food APG/APM Table

Long Term Goal: ***By 2008, provide scientific tools to OPP/OPPTS that can be used to characterize, assess, and manage risks across the exposure-to-dose-to-effects continuum in implementing the FQPA requirements***.

ANNUAL PERFORMANCE GOALS, MEASURES, AND MILESTONES		YEAR	LAB/ CENTER	INTERNAL/ EXTERNAL
APG 32:	**Deliver state-of-the-science tools (methods, models, approaches) and quality exposure data for characterizing aggregate risks from exposure to pesticides to OPP in order to reduce uncertainty in risk assessments under FQPA**	**FY 03**		**Internal**
59	Report on pharmacokinetics of four neurodevelopmental toxicants	03	NCEA	
30	Complete field monitoring study (CTEPP) to evaluate aggregate exposures of 260 young children in homes and daycare centers to persistent organic pollutants	03	NERL	
244	Peer Reviewed Design for Field Study to Evaluate Protocols for obtaining reliable data on Children's Exposure to Pesticides.	03	NERL	
253	Analysis and report on factors for children's exposure to pesticides that may lead to high-level, short-term exposure to pesticides.	03	NERL	
153	Perform binary mixture studies using organophosphates and carbamate pesticides. Develop guidance and specific methods for performing these types of interaction studies	03	NHEERL	
8	Report on a STAR sponsored workshop on temporal variability in pesticide exposure modeling and assessment to update OPPTS on the progress of monitoring studies	03	NCER	
APG 37:	**Analysis of needs and research strategy for developing tools and data to characterize cumulative exposures/risks for pesticides**	**FY 04**		**Internal**
215	Research plan for developing and evaluating exposure data and tools to improve cumulative risk assessments for pesticides conducted by the Agency and others in the scientific community.	04	NERL	
228	*Using current modeling tools, identify exposure measurement studies to provide critical data needed for exposure models that will be used by the Agency to conduct cumulative risk assessments. (Also Human Health)*	*04*	*NERL*	

APG 38:	**Develop framework and analysis of research needs for using PBPK data and models in risk assessment.**	**FY 04**		**Internal**
228	*Complete External Review Draft of a report on the use of pharmacokinetic data in risk assessments for children (Human Health - Susceptibility)*	*03*	*NCEA*	
128	*Workshop report on application of PBPK modeling to quantify PK variance as a component of uncertainty factors in risk assessment (Human Health - Susceptibility)*	*04*	*NCEA*	
98	External review draft of a report on the use of PBPK data and models in risk assessment	04	NCEA NERL NHEERL NCER	
7	*Summary of research on PK/PD modeling to account for inter-species extrapolation in risk assessment (Human Health - Harmonization)*	*04*	*NHEERL*	
182	*Development of pharmacokinetic/pharmacodynamic model to quantitate biomarkers of exposure for organophosphate insecticides (Human Health - Harmonization)*	*04*	*NCER*	
APG 42:	**Provide sound science that supports the August 2006 reassessment of pesticide tolerances**	**FY 05**		**External**
63	*NHEXAS Exposure Factors Data Analysis. Complete an External Review Draft of a report analyzing NHEXAS data for use in updating the Exposure Factors Handbook (Human Health - Aggregate/Cumulative)*	*03*	*NCEA*	
107	*External review draft of an updated Exposure Factors Handbook for Children, incorporating new data from ORD-supported studies (Human Health-Susceptibles)*	*04*	*NCEA*	
366	Complete an external review draft of an EPA report or submit a journal article analyzing pesticides data collected through NHANES from 1999 and 2000	04	NCEA	
225	Develop next generation models to estimate exposure and dose to pesticides and other environmental contaminants so that EPA can produce improved exposure and risk assessments.	04	NERL	
226	Provide refined methods to the Agency and scientific community for measuring children's exposures to pesticides and other environmental contaminants.	04	NERL	
218	*Conduct analysis of the "Children Total Exposure to Pesticides and Persistent Organic Pollutants (including EDCs) Study" to estimate aggregate exposures and identify critical exposures factors that can be used by the Agency to improve exposure and risk assessments. (Also Human Health and Emerging Risks, EDCs)*	*04*	*NERL*	

9	*Develop prototype version of Source Modules for the overall source-exposure-effect aggregate modeling, for indoor sources/source types, using available models/data. Include non-indoor sources as possible. (Human Health, Aggregate/Cumulative)*	*04*	*NRMRL*	
APM	*Develop model components to estimate exposure and dose to environmental contaminants for EPA to use in conducting assessments of aggregate exposure and risk. (Human Health - Aggregate/Cumulative)*	*05*	*NERL*	
APM	Provide OPPTS with the available NERL sponsored children's exposure data and tools for assessing aggregate exposure to residential-use pesticides in support of the August 2006 reassessment.	05	NERL	
APG 43:	**Dose response research that addresses cumulative exposures/risks and the hypothesis of dose additivity for pesticide mixtures**	**FY 06**		**Internal**
66	*Complete an external review draft internal workshop report on common modes of action for different toxic effects (Human Health - Harmonization)*	*03*	*NCEA*	
80	*Complete an External Review Draft report on the effect of pesticide mixtures on immunologic response in mice at different life stages (Human Health - Susceptibles)*	*03*	*NCEA*	
55	*Provide dosimetry methods and measurements to identify modes of action for inhalation exposure with focus on the nasal tract (Human Health, Susceptibles)*	*03*	*NCEA*	
169	Evaluate the individual and cumulative effects of exposure to pesticides and toxic substances with antiandrogenic activity vs those that block fetal steroidogenesis	04	NHEERL	
170	Develop and use novel statistical models of dose-additivity for behavioral and neurochemical interacting of organophosphate pesticides (common mode of action) in adult rats. Provide data regarding default assumption of additivity	04	NHEERL	
171	Provide data regarding the default assumption of additivity for a mixture of four or more carbamate pesticides	04	NHEERL	
172	Report of studies on modeling of dose-response curves of prototypic chemicals having similar or different modes or mechanisms of action	04	NHEERL	
APM	Compare nature of the interactions of organophosphate pesticides in adult and developing rats	05	NHEERL	
APM	Conduct studies to provide the basis to compare acute and subchronic toxicities of a mixture of high volume usage carbamate pesticides to better understand whether acute interactions predict the profile of interactions following repeated exposures	06	NHEERL	

APM	Evaluate age-related differences in response to repeated pesticide exposure, using behavioral and neurochemical endpoints	06	NHEERL	
APM	Evaluate age-related differences in response to repeated pesticide exposure, using behavioral and neurochemical endpoints	06	NHEERL	
APG 6-02:	**Provide risk assessors and managers with approaches for using PBPK data and models in risk assessment**	**FY 06**		**Internal**
Pend #	Collect pharmacokinetic data on pesticides for use in interpreting biological marker information for use by pesticide registrants responding to OPPTS requirements	04	NCER	
APM	Report on a method to derive concentrations of contaminants in target organs to support cumulative risk assessments	05	NCEA	
APM	Provide technical and regulatory support, consultation, and review on scientific issues related to risk assessment to OPPTS	05	NCEA	
APM	Evaluate biomarkers and pharmacokinetic data for their applicability to the pesticide risk assessments required under the Food Quality Protection Act (FQPA)	05	NCER	
APM	Report on approaches for using PBPK data and models in risk assessment	06	All (NCEA lead)	
APM	Analysis of existing children's exposure data to identify important factors for characterizing cumulative exposure to pesticides and other environmental contaminants	06	NERL	
APM	*Develop PBPK models for using exposure, biomarker, and pharmacokinetic data in risk assessments. (Also Human Health)*	*06*	*NERL*	
APG 7-01:	**Evaluate 10X safety factors for new pesticides for aggregate exposure/risk**	**FY 07**		**Internal**
48	*External review draft report on framework for conducting risk assessments for children as a sensitive population (Human Health, Susceptibility)*	*02*	*NCEA*	
70	*Provide state of science paper on chemicals in breast milk as related to risk assessment (Human Health, Susceptibles)*	*03*	*NCEA*	
229	*Conduct modeling analysis of NERL's children studies to identify key uncertainties and data gaps for use by EPA and the science community to plan future measurement studies that specifically address these gaps. (Also Human Health and Emerging Risks, EDCs)*	04	NERL	
APM	*External review draft on conducting risk assessments for children as a sensitive subpopulation (Human Health, Susceptibles)*	*05*	*NCEA*	

APM	*Issue papers on biomarkers of exposure & effect in children (Human Health, Susceptibles)*	*06*	*NCEA*	
APM	External review draft of a report on exposure factors for pesticides for use by OPPTS	06	NCEA NERL NCER	
APM	Provide OPPTS with an analysis of aggregate exposures of infants and toddlers in homes to pesticides and other environmental contaminants to fill critical data gaps and identify key aggregated exposure and 10X safety factor research needs. (Also Human Health and Emerging Risks, EDCs)	06	NERL	
APM	*Incorporate results/publications from NHEXAS Data Analysis Strategy into HEDS, ORD's publically-available Human Exposure Database System (Human Health, Aggregate/Cumulative)*	*06*	*NERL NCEA NCER*	
APM	Complete first year of field monitoring study of longitudinal aggregate exposures for infants and toddlers that will be used to evaluate measurement approaches and to provide the Agency with critical data to substantially improve aggregate exposure assessments for young children to pesticides and other environmental contaminants. (Also Human Health and Emerging Risks, EDCs)	06	NERL	
APM	Develop dose response data on the adverse developmental effect(s) of exposure to phthalates to address the 10x safety factor	06	NHEERL	
APM	Complete longitudinal exposure study and conduct analyses to estimate aggregate exposures, to evaluate exposure algorithms, to evaluate approaches for measuring exposure and to identify critical exposure factors that can be used by the Agency to improve exposure and risk assessments. (Also Human Health and Emerging Risks, EDCs)	07	NERL	
APG 8-01:	**Develop tools and data to characterize cumulative exposures/risks for current use and emerging pesticides, including lifestage and temporal variability**	**FY 08**		**Internal**
230	*Provide innovative, low burden exposure research tools that can be used by the Agency and the scientific community in designing and implementing the National Children's Study. (Also Human Health and Emerging Risks, EDCs)*	*04*	*NERL*	
Pend #	*Evaluate exposure intervention strategies for reducing pesticide exposures among children in agricultural communities (Human Health - Susceptibles)*	*04*	*NCER*	

APM	Draft risk management protocol for assessing risks to selected pesticides from drinking water	05	NRMRL	
APM	Develop, evaluate, and provide improved field and laboratory exposure methods to ORD for use in characterizing cumulative exposures to one or more selected classes of current use pesticides	06	NERL	
APM	Complete first year of field monitoring study of longitudinal aggregate exposures for infants and toddlers that will be used to evaluate measurement approaches and to provide the Agency with critical data to substantially improve aggregate exposure assessments for young children to pesticides and other environmental contaminants. (Also Human Health and Emerging Risks, EDCs)	06	NERL	
APM	Develop experimental database of pharmacokinetic parameters for pyrethroid pesticides after oral and dermal exposure	06	NHEERL	
APM	Develop experimental database of neurotoxicological effects for pyrethroid pesticides after oral and dermal exposure	06	NHEERL	
APM	Integrate pharmacokinetic data with neurotoxicology data of pyrethroid pesticides for pharmacodynamic modeling	06	NHEERL	
APM	Develop experimental database of pharmacokinetic interactions of binary mixtures and intermittent exposure of pyrethroid pesticides	06	NHEERL	
APM	Provide data on the aggregate toxicity of dermally and orally administered methyl carbamates using neurobehavorial and biochemical endpoints in adult rats	06	NHEERL	
APM	Evaluate the temporal variation in the exposure of selected populations to pesticides based on longitudinal case studies of pesticide exposure	06	NCER	
APM	Complete longitudinal exposure study and conduct analyses to estimate aggregate exposures, to evaluate exposure algorithms, to evaluate approaches for measuring exposure and to identify critical exposure factors that can be used by the Agency to improve exposure and risk assessments. (Also Human Health and Emerging Risks, EDCs)	07	NERL	
APM	Perform binary mixture studies using organophosphates and carbamate pesticides in young rats. Develop guidance and specific methods for performing these types of interaction studies	07	NHEERL	
APM	*Integrated DBP mixtures research: synthesis of toxicological data (reproductive/developmental) from the multilab mixture study (Also Clean and Safe Water)*	*07*	*NHEERL*	
APM	Publish longitudinal data on the temporal variation in the exposure of selected populations to pesticides in a publically available format	07	NCER	

APM	Develop, evaluate, and provide improved biomonitoring methods to ORD for use in future field studies for assessing cumulative exposures to one or more selected classes of current use pesticides	08	NERL	
APM	*Demonstrate the use of NERL's human exposure modeling tools and databases to assess young children's exposures to pesticides, EDCs, and other environmental contaminants. (Also Human Health and Emerging Risks, EDCs.)*	*08*	*NERL*	
APM	*Evaluate developmental and reproductive toxicants that act by the same modes of action but different endocrine mechanisms on both male and female offspring (Also Emerging Risks, EDCs)*	*08*	*NHEERL*	
APM	Summarize results comparing response of adult and young animals to binary mixtures of organophosphates and carbamate	09	NHEERL	
APM	Revised risk management protocol for assessing risks to pesticides in drinking water	08	NRMRL	
APM	*Incorporate Source Module into ORD source-aggregate exposure-effects model. Evaluate and document use of the Source Module for Program Offices and public (Human Health, Aggregate/Cumulative)*	*08*	*NRMRL*	
APG 8-02:	**Develop guidance for using PBPK data and models to support risk assessments**	**FY 08**		**Internal**
APM	Provide technical and regulatory support, consultation, and review on scientific issues related to risk assessment to OPPTS	06	NCEA	
APM	Summary of biomarker studies utilizing pharmacokinetic data to interpret their applications to cumulative and aggregate risk assessment for inclusion in NCEA and OPPTS guidance	07	NCER	
APM	Final guidance for using PBPK data and models in support of risk assessment	08	All (NCEA lead)	